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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,281	KOHLER, HEINZ	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/05 has been entered.

2. Claims 1-40 are pending.

3. Claims 1-20 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 21-40, drawn to an antigen-binding fusion protein, are being acted upon in this Office Action.

5. Claims 20-40 are objected to under 37 CFR 1.821(d) because SEQ ID NO: is required.

6. The International Search Reports on PTO 1449, filed 8/10/05 have been considered but crossed out because they are inappropriate to be printed on an issued patent.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the human C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances the immunogenicity of the claimed anti-idiotypic antibody, **does not** reasonably provide enablement for any fusion protein as set forth in claims 21-40. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody crosslinked to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less which peptide is a homolog or non-human C3d peptide (see page 12-13 of specification). The specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not teach how to make and use any antigen-binding fusion protein as set forth in claims 28-35 because there is a insufficient guidance as to the binding specificity of the antibody correlated with the structure such as the CDRs of the heavy and light chain in the fusion protein. Further, there is also a lack of guidance as to the structure of the peptide in the fusion protein that has "homophilic activity", immunostimulating activity and/or membrane transporting activity without the amino acid sequence. A peptide in the claimed fusion protein with homophilic activity, immunostimulatory activity and/or transport activity without the amino acid sequence has no structure. There is insufficient guidance as to the structure of the peptide without the amino acid sequence, let alone the length of the peptide wherein the peptide has inverse hydropathicity, has immuno-stimulatory activity, membrane transport activity or homophilic binding activity. Without knowing the amino acid sequence (the length) of the peptide in the fusion protein, one skilled in the art cannot make any "inverse hydrophathicity within the length of said peptide".

With regard to claims 36-40, a reference to the amino acid sequence (SEQ ID NO) of the human C3d containing residues 1217-1232 is required. Further, the specification does not teach any and all "non-human C3d", "homologue" to human C3d residues at position 1217-1232 without any the amino sequence. There is a lack of guidance as to as to which amino acids within the sequence from which mammal correlates with residues 1217-1232 of which human C3d, much less which addition, deletion, substitution and combination thereof maintains the function of such peptide in the claimed fusion protein as that of human C3d at position 1217-132.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

With regard to antibody comprises a light chain "**or**" heavy chain immunoglobulin" as recited in claims 22, 27, 29, 30, 33 and 34, there is a lack of guidance and working example demonstrating that antibody comprises either light chain or heavy chain is capable of binding to any antigen. The state of the antibody art as exemplified by Harlow et al is such that antibody binding to antigen requires both the variable domains of heavy *and* light chains to form an antigen binding site (see page 8-9, Figure, in particular).

Given the unlimited number of fusion protein comprising undisclosed antibody binding specificity and undisclosed peptide, there is insufficient working example demonstrating that claimed fusion protein comprising any peptide when fused to any antibody will resulted in immunostimulatory activity, membrane transport activity, and/or homophilic activity. Given the unlimited number of undisclosed antigen binding fusion protein, it is unpredictable which undisclosed peptide and antibody in the claimed fusion protein would be useful for which purpose.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/28/05 have been fully considered but are not found persuasive.

Applicants' position is that while one of the preferred embodiments of the present invention is a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide of SEQ ID NO: 1 derived from the C3d region 1217-1232, the specification clearly recites that other active peptides can be inserted into other antibodies. Specifically, column 5, lines 24-39 of U.S. Patent No. 6,238,667 (which is the parent patent of this application and which specification is incorporated into this application) further recites that peptides of the invention may have a biological activity, may comprise immunogenic epitopes, may be a hormone, ligand, etc. that may be bound to an antibody which is a full-length immunoglobulin molecule or a variable domain fragment of an antibody. See also page 12, lines 17-26 and 14, lines 1-9 of the specification of the present application.

It is noted that the 09/070,907 application, now US pat 6,238,667 B1, teaches a method of affinity crosslinked a peptide to an antibody. The '667 patent does not each any fusion protein comprising any peptide fused to any antibody. Further, none of the claims recited a fusion protein comprising a peptide consisting of SEQ ID NO: 1 fused to an antibody. The only peptide

that has homophilic, immunostimulatory and membrane transport is the peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less any peptide is any homolog or non-human C3d peptide (see page 12-13 of specification). The specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. Even this particular fusion protein has been published by Dempsey et al in Science 271: 348, 1996. The specification discloses crosslinking 13mer peptide SEQ ID NO: 1 derived from the C3d region 1217-1232 with anti-CEA antibody enhances the immunity of the anti-CEA antibody (see page 14-16, Example 1). It is noted none of the working examples shows any fusion protein comprising any peptide homolog to human C3d region 1217-1232 and any antibody, much less the peptide is either N terminal of any antibody heavy chain or antibody light chain or the peptide is located within the heavy or light chain.

In response to applicant's argument as to why the fourteen (14) U.S. patents recited at page 4, lines 7-20, together with the examples and procedures recited at pages 10-14, do not provide sufficient guidance to one of ordinary skill in the art to make the claimed fusion protein, the specification as filed merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention without the *structure* correlated with functions of the fusion protein discussed above. A peptide having membrane transport activity or a peptide having homophilic activity or a peptide having immunostimulatory without the amino acid sequence has no structure.

As to why the detailed section called "Production of a Fusion Gene" recited at pages 10-14 and the examples of the specification do not provide one of ordinary skill in the art sufficient guidance to make the claimed fusion protein, this is because of the following reasons: (1) the claims encompasses any fusion protein comprising any antibody and any peptide, (2) the specification does not provide any guidance as to the structure correlated with function of any fusion protein, any antibody such as the binding specificity correlated with the structure such as the CDRs of the heavy and light chain of any antibody, and the structure of the peptide correlated with the cited activities without the amino acid sequence. (3) The specification discloses only C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. Even this particular fusion protein has been published by Dempsey et al in Science 271: 348, 1996. One skilled in the art reading the specification would wonder what exactly is applicant's invention. The specification discloses **crosslinking** 13mer peptide SEQ ID NO: 1 derived from the C3d region 1217-1232 with anti-CEA antibody to enhance the immunity

of the anti-CEA antibody (see page 14-16, Example 1). One skilled in the art would recognize conjugating an antibody to a peptide is hardly a fusion protein. (4) It is noted that none of the working examples show any fusion protein comprising any peptide homolog to human C3d region 1217-1232 and any antibody, much less the peptide is either N or terminal of any heavy or light chain or the peptide is located internally or inside the nucleic acid encoding the heavy or light chain immunoglobulin. (5) the specification does not which antibody in the fusion protein comprising **either** heavy or light chain still binds to the antigen. (6) Given the unlimited number of peptide and antibody in the claimed fusion protein, it is unpredictable which undisclosed peptide has which activity, which antibody has binding specificity to which cellular receptor and what effect does not the claimed fusion protein has.

9. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and all (1) antigen-binding fusion protein comprising (2) any antibody, and (3) any peptide having homophilic activity, (4) any antibody in the fusion protein is any antibody that is specific for any cellular receptor on normal cell or tumor cell, (5) any peptide in the fusion protein is any peptide has inverse hydropathicity within the length of said peptide, (6) any peptide in the fusion protein is any immunostimulatory peptide of any peptide has any membrane transport activity, (7) any peptide is derived from any non-human C3d region homologous to human C3d residues at position 1217-1232 and ranges from about 10 to about 16mer and (8) any peptide is derived from human C3d region homologous to human C3d residues at position 1217-1232 and ranges from about 10 to about 16mer without the reference sequence (SEQ ID NO).

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody crosslinked to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less any peptide is any homolog or non-human C3d peptide (see page 12-13 of specification). The

specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not disclose any antigen-binding fusion protein as set forth in claims 28-35 because there is inadequate written description about the structure associated with function of the claimed fusion protein. The specification does not disclose the binding specificity of any antibody that correlated with the structure such as the CDRs of the heavy and light chain in the fusion protein. The specification does not disclose the structure of the peptide in the fusion protein that has "homophilic activity", immunostimulating activity and/or membrane transporting activity without the amino acid sequence. A peptide in the claimed fusion protein with homophilic activity, immunostimulatory activity and/or transport activity without the amino acid sequence has no structure.

With regard to claims 36-40, the recitation of a human C3d peptide containing residues 1217-1232 must reference to an amino acid sequence with (SEQ ID NO). Further, the specification does not describe any and all "non-human C3d", "homologue" to human C3d residues at position 1217-1232 without any the amino sequence. Given the unlimited number of peptide derived from "non-human C3d", and "homologue" to human C3d containing residues 1217-1232, the peptide in the fusion protein is not adequately described without the amino acid sequence. Given the unlimited number of antigen-binding fusion protein, there is insufficient written description about the cellular receptor on normal cell and the cellular receptor on tumor cell that the claimed antigen-binding fusion protein binds. Since the individual component such as the antibody, and the peptide within the fusion protein are not adequately described, it follows that any antigen-binding protein is not adequately described.

Finally, given the lack of an additional species of antigen-binding fusion protein, peptide, antibody that binds to any cellular receptor on normal or tumor cell, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/28/05 have been fully considered but are not found persuasive.

Applicants' position is that the specification does not merely naming a single peptide or species as in the case of the University of California's patent. Further, the specification of the present application sufficiently describes the fusion proteins of the claimed invention. The claim terms in the present application are not unknown biological materials that ordinary skilled in the ad would easily miscomprehend instead are deemed to readily convey distinguishing information concerning the identity of the peptides as well as antibodies. Thus, as acknowledged by the court in Lilly, the specification of the present application provides adequate written description of a genus of the fusion protein by means of a recitation of a representative number of peptides and antibodies, defined by fusion protein, falling within the scope of the genus. In contrast to the University of Rochester case, the specification of the present application provides adequate description of how to create the claimed fusion protein. The fusion proteins of the claimed invention include a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activities, where the peptide does not interfere with antigen binding. Further, one of ordinary skill in the art can readily determine whether the claimed peptide comprises one or more of the aforementioned activities. Similarly, the present invention as presently claimed includes any particular antibody binding specificities as well as any peptides possessing one or more of the aforementioned activities so long as the peptide does not interfere with antigen binding. Thus, the claimed invention can be used in a myriad of combinations, the details of which are known to those skilled in the art. The specification clearly provides examples the necessary guidance to apply the invention to various combinations under the practice of the invention.

Contrary to applicant's assertion that the specification provides examples the necessary guidance to apply the invention to various combinations under the practice of the invention, the specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody crosslinked to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16). The only peptide that has homophilic, immunostimulatory and membrane transport is the peptide derived from C3d region 1217-1232 of human C3d. The specification does not teach any other peptide, much less any peptide is any homolog or non-human C3d peptide (see page 12-13 of specification). The

specification discloses fusing C3d peptide as adjuvant to hen egg lysozyme (HEL) to enhance the immunogenicity of the immunogen HEL. The HEL immunogen is not an antibody.

The specification does not disclose any antigen-binding fusion protein as set forth in claims 28-35 because there is inadequate written description about the structure associated with function of the claimed fusion protein. The specification does not disclose the binding specificity of any antibody that correlated with the structure such as the CDRs of the heavy and light chain in the fusion protein. The specification does not disclose the structure of any peptide in the fusion protein that has "homophilic activity", immunostimulating activity and/or membrane transporting activity without the amino acid sequence. A peptide in the claimed fusion protein with homophilic activity, immunostimulatory activity and/or transport activity without the amino acid sequence has no structure, much less function. With regard to claims 36-40, the recitation of a human C3d peptide containing residues 1217-1232 must reference to an amino acid sequence with (SEQ ID NO). Further, the specification does not describe any and all "non-human C3d", "homologue" to human C3d residues at position 1217-1232 without any the amino sequence. Given the unlimited number of peptide derived from "non-human C3d", and "homologue" to human C3d containing residues 1217-1232, the peptide is not adequately described without the amino acid sequence. Given the unlimited number of antigen-binding fusion protein, there is insufficient written description about the cellular receptor on normal cell and the cellular receptor on tumor cell that the claimed antigen-binding fusion protein binds. Since the individual component such as the antibody, and the peptide within the fusion protein is not adequately described, it follows that any antigen-binding protein is not adequately described.

The specification as filed does not provide written description support for the structural characteristics that define the claimed antigen-binding fusion protein. The skilled artisan cannot envision the contemplated the detailed chemical structure of the claimed fusion protein any antibody and peptide as well as nucleic acid encoding said fusion protein. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating or making it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. In Fiers v. Sugano, it was stated: "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and

reference to a potential method for isolating it; what is required is a description of the DNA itself" (26 USPQ2d 1601 at 1606). Thus, the instant specification does not adequately describe, and therefore cannot adequately teach how to make, the claimed invention. "It is not sufficient to define the fusion protein by its principal biological activity, e.g. peptide having homophilic activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 29, 37, 38, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "human C3d residues at position 1217-1232" in claims 29, 37, 38, 39 and 40 is ambiguous and indefinite because one of the ordinary skill in the art cannot appraise the metes and bound of the claimed "position 1217-1232" without reference to an amino acid sequence (SEQ ID NO).

12. The filing date of the instant claims is deemed to be the filing date 5/29/01 of the instant application as the parent application 09/070,907 is drawn only to a method of affinity *cross-linking* a peptide to an antibody by photo-chemically activating an azido compound, and thus does not support the claimed limitations an antigen-binding *fusion protein* comprising an antibody and a peptide having a homophilic activity of the instant application.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 21-28 and 30-35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/17625 (June 13, 1996; PTO 892).

The WO 96/17625 publication teaches an antigen binding fusion protein comprising an antibody such as single chain scFv antibody or antibody to CD21 (also known as CR2 or complement receptor 2 found on B cells and dendritic cells) or CD19 (see pages 21-23, in particular) fused to a peptide such as C3d (see paragraph bridging page 6-7, in particular) wherein the reference peptide does not interfere with antigen binding (see page 7, lines 5-9, in particular). The reference peptide is fused to either the C-terminal or the N-terminal end of the fusion protein such as the heavy or light chain of immunoglobulin such as Fab, F(ab')2, scFv (see paragraph bridging page 21-22, page 6in particular). The reference peptide inherently has homophilic activity because the claimed peptide in the claimed fusion protein appears to be the same as that of the prior art. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference fusion protein is created by recombinant DNA technology by gene fusion (see page 22, line 13, page 23, line 22-25, in particular). The reference nucleic acid encoding the peptide C3d is fused to a nucleic acid sequence encoding the reference antibody in an expression vector (see paragraph bridging page 7 and 8, pages 8-9, in particular) where the peptide is located internally to the antibody such as within the constant region of a heavy or light chain of the antibody. The reference antibody or the binding fragment thereof (variable domain thereof) binds to a specific cellular receptor such as CD21 or CD19 on B cell. The reference peptide fragment inherently has inverse hydropathicity since it is also immunogenic and the claimed peptide in the fusion protein appears to be the same as that of the prior art (see page 5, lines 7-9, in particular). The reference peptide inherently has membrane transport activity since C3d binds to complement receptor such as CR2. Thus, the reference teachings anticipate the claimed invention.

15. Claims 32-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerstmayer et al (J Immunology 158: 4584-4590, May 1997; PTO 892).

Gerstmayer et al teach an antigen-binding fusion protein comprising an antibody such as single chain antibody scFv (FRP5) that binds specifically to erbB2, and a peptide such as fragment of B7-2225 that has a membrane transport activity such as localizes the fusion molecule to the surface of ErbB-2 expressing cells and does not interfere with antigen binding of the reference antibody (see page 4585, col. 1, first paragraph, in particular). The reference fusion protein where the peptide is fused to the N-terminal of the reference light chain or heavy chain (see page 4586, col. 1, Figure A, in particular). The reference antibody is specific for a erbB receptor on a tumor cell such as adenocarcinomas (see page 4585, col. 2, binding assays, page 4585, col. 2, full paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,314,995 (of record, May 1994, PTO 892).

The '995 patent teaches a fusion protein made up of an antibody such as anti-tumor antigen L6 antibody and peptides such as IL-2, and IL6 having a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). The reference IL-2 peptide is connected to a site such as the Fc region of the reference antibody, which is the C terminal of the heavy chain of the antibody that does not interfere the reference antibody from binding to tumor cells. The reference fusion protein is created by a process comprising the steps of creating a fusion product using a nucleic acid sequences encoding the reference antibody and the reference peptide (See Fig 6A-10, column 3, Construction of recombinant genes encoding antibody fusion proteins, in particular). The '995 patent teaches that the reference antibody is the variable region of the light and heavy chain of the anti-tumor antigen monoclonal antibody (See column 2, line 52, lines 55, in particular). The reference antibody based fusion proteins are useful as a method of delivering biologically active ligand molecules to the target cells or tissues and offers the advantage of decreasing systemic exposure to lymphokines and minimizing toxic effects (See column 8, lines 21-26, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/28/05 have been fully considered but are not found persuasive. Applicants' position is that claim 28 has been amended. The cited document fails to

disclose a antigen-binding fusion protein comprising (1) an antibody and (2) a peptide having immuno-stimulatory activity, wherein said peptide does not interfere with antigen binding, and wherein said antibody comprises a light chain or heavy chain immunoglobulin molecule and wherein said peptide is attached to the C-terminal or the N-terminal of said light chain or heavy chain immunoglobulin molecule.

In response, the amended claim 28 does not overcome this rejection because the '995 patent teaches a fusion protein made up of an antibody such as anti-tumor antigen L6 antibody and peptides such as IL-2, and IL6 having a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). The reference IL-2 peptide is fused to the Fc region of the reference antibody, which is the C terminal of the heavy chain of the antibody that does not interfere the reference antibody from binding to tumor cells. The "C-terminal of a heavy chain immunoglobulin molecule" is the same as the Fc region of the antibody. Although claim 28 has been amended, the amended claim 28 still recites any fusion protein comprising any antibody fused to any peptide so long the peptide has immunostimulating activity.

17. Claims 28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,698,679 (of record, Dec 1997, PTO 1449).

The '679 patent teaches an antigen-binding fusion protein comprising an antibody that binds specifically to a cellular receptor such as CD40 on normal cell such as APC cells and B cells fused to an immunogenic peptide such as ovalbumin 326-337 (See entire document, column 25, example 2, column 8, lines 43-50, in particular). The '679 patent teaches the reference peptide is located within the CDR1 variable domain of a light chain, which is N terminal of the reference light chain, such that the immunotargeting and presentation function of the immunoglobulin fusion protein are not impair (see col. 27, Example 4, col. 23, line 47-54, in particular). The reference CDR1 light chain is the same as the claimed N-terminal of immunoglobulin light chain. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/28/05 have been fully considered but are not found persuasive. Applicants' position is that claim 28 has been amended. The antigen-binding fusion of amended claims 28 and 31 are clearly different from the fusion protein of Nemazee. The cited document fails to disclose a antigen-binding fusion protein comprising (1) an antibody and (2) a peptide having immuno-stimulatory activity, wherein said peptide does not interfere with antigen

binding, and wherein said antibody comprises a light chain or heavy chain immunoglobulin molecule and wherein said peptide is attached to the C-terminal or the N-terminal of said light chain or heavy chain immunoglobulin molecule.

In response, amendment to claim 28 does not overcome this rejection because the reference CDR1 light chain is the same as the claimed N-terminal of immunoglobulin light chain. The '679 patent teaches an antigen-binding fusion protein comprising an antibody that binds specifically to a cellular receptor such as CD40 on normal cell such as APC cells and B cells fused to an immunogenic peptide such as ovalbumin 326-337 (See entire document, column 25, example 2, column 8, lines 43-50, in particular). The reference peptide is located within the CDR1 variable domain of a light chain, which is N terminal of the reference light chain, such that the immunotargeting and presentation function of the immunoglobulin fusion protein are not impair (see col. 27, Example 4, col. 23, line 47-54, in particular). Further, although claim 28 has been amended, the amended claim 28 still recites any fusion protein comprising any antibody fused to any peptide so long the peptide has immunostimulating activity.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 21-22, 29, 32-33 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/17625 (June 13, 1996; PTO 892) in view of Lambris et al (Proc Natl Acad Sci 82: 4235-4239, June 1985; PTO 1449) and Dawa et al (Dev Biol Stand 92: 3-11, 1998; PTO 892).

The teachings of the WO 96/17625 publication have been discussed supra.

The invention in claims 36-40 differs from the teachings of the reference only in that the reference antigen-binding fusion protein wherein the peptide is derived from a human C3d region homologous to the human C3d residues at position 1217-1232 and ranges from about 10 to about 16mer.

Lambris et al teach various peptides such as KNRWEDPGKOLYNEA (P16) or LYNVEATSYA (P10) from C3d (see page 4237, Table 2, in particular). The reference peptide P16 is identical to the human C3d residues 1217-1232 (see page 4238, col. 1, last paragraph,

abstract, in particular) and is 16 amino acids in length (16mer). The reference peptide P10 is homologous to the human C3d residues at position 1217-1232 and is 10 amino acids in length, which are about 16 amino acids in length. Both peptides bind to CR2, which is a receptor on B cell (B lymphocyte) and blocks by antibody mAb 130 (see Table 2, page 4237, Discussion, page 4238, col. 1, in particular). Lambris et al further teach the homologue of the reference peptide such as peptide 1218-1236 of mouse which is identical to the human (see page 4238, col. 1, last paragraph, in particular).

Dawa et al teach the adjuvant effect of C3d. Complement activation generates C3d which binds CR2 (CD21) on FDC, and B cells, thereby stimulating proliferation of B cells and generation of memory B cells and targeting antigen to the antigen presenting cell such as dendritic cells favor cell-mediated immunity.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the C3d in the fusion protein as taught by the WO 96/17625 publication for the peptide such as P16 or P10 as taught by Lambris et al to target the fusion protein to the CR2 on B cells or dendritic cells as taught by Dawa et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine the references because C3d which binds CR2 (CD21) on FDC, and B cells, stimulates the proliferation of B cells and generation of memory B cells and targeting antigen to the antigen presenting cell such as dendritic cells favor cell-mediated immunity as taught by Dawa et al. Lambris et al teach peptides such as KNRWEDPGKOLYNEA (P16) or LYNVEATSYA (P10) from human C3d and mouse homolog bind to CR2 on B cells and APC (see page 4238, col. 1, last paragraph, in particular). The WO 96/17625 publication teaches C3d enhances the immunogencity of the reference antibody (see page 5, lines 7-9, in particular).

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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